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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,461	04/17/2001	Robert Leroy Heinrikson	6309.N CP	8815

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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

KC

Office Action Summary	Application No.	Applicant(s)	
	09/836,461	HEINRIKSON ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,23-31 and 33-46* is/are pending in the application.

4a) Of the above claim(s) *1-20 and 34-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-31,33,45 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants continue to misnumber claims. According to applicant's response claims 1-22, 34-46 remain withdrawn and claims 21-22 are cancelled. Accordingly claims presented for examination include 23-31, 33, 45 and 46. Claim 32 has been presented as cancelled.

Sequence Compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that applicants fail to recite corresponding SEQ ID NO for sequences depicted in figures or figure description. See particularly 37 CFR 1.821(d). In response to the previous Office action, applicants have requested the Examiner that the above formality be held in abeyance until the application is in condition for allowance. However, Examiner has indicated the above requirement for reasons of record.

Specification

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Applicants have numbered two successive claims as 29. Newly presented claims have been numbered as 45 and 46 as opposed to 47 and 48. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 26-29, 29-31, 33, 45-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of the polypeptide with SEQ ID NO:2 or amino acids 42-534 of SEQ I D NO:2 as heparanase enzyme, does not reasonably provide enablement for use of polypeptides or compositions comprising amino acids 42 through 129 or 42 through 161 or 130 through 534 or 162 through 534 of SEQ ID NO:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 23, 26-29, 29-31, 33, 45-46 are so broad as to encompass any or all polypeptides comprising amino acids 42 through 129 or 42 through 161 or 130 through 534 or 162 through 534 of SEQ ID NO:2 including variants, mutants and recombinants. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the use of fragments broadly encompassed by the claims. Since the amino acid sequence of a protein

determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The disclosure is limited to teaching the nucleotide and encoded amino acid sequence SEQ ID NO:2 or amino acids 42-534 having heparanase activity. It would require undue experimentation by the skilled artisan to use the claimed polypeptides with an undefined function/activity. The specification is limited to teaching the making and use of SEQ ID NO: 2 or amino acids 42-534 of SEQ ID NO:2 as a heparanase but provides no guidance with regard to the making of variants fragments or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to make and use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for a large number of variants, mutants or fragments, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited

in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass the use of specific polypeptide fragments of SEQ IUD NO:2 because the specification does not establish: (A) regions of the protein structure which may be modified without effecting heparanase activity; (B) the general tolerance of heparanase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying amino acid residues in SEQ ID NO:2 with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including fragments of SEQ ID NO:2 without showing that such fragments have activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of fragments of SEQ ID NO:2 having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action, applicants have amended the claims by deleting reference to "human heparanase-II". This mainly appears to be due to the confusion with respect

to the 35 U.S.C. 112, 2nd paragraph rejection for the recitation of "heparanase-II". In response to that rejection all that applicants had to do was reiterate that the difference between the known heparanase in the prior art and the instant heparanase is in the amino acid sequence information. However, applicants have deleted all references to the term which described the activity of the polypeptides. Furthermore, in response to the previous rejection under 35 U.S.C. 112, Ist paragraph, for lack of enablement, applicants argue that Examiner grossly misstates the law and have argued that Federal Circuit specifically validated the proposition that a disclosure that utilizes routine screening using well known procedures to make the invention constitutes enabling disclosure and recite the case of *Hybritech, Inc. vs Monoclonal antibodies Inc.* It is not clear to the Examiner as to how the above case is relevant to the instant situation. Those skilled in the art would not how to use the claimed polypeptide fragments without knowing what activity the polypeptides have. Hence the above rejection is maintained.

Claims 23, 26-29, 29-31, 33, 45-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 23, 26-29, 29-31, 33, 45-46 are directed to polypeptides and polypeptide fragments. Claims 23, 26-29, 29-31, 33, 45-46 are rejected under this section of 35 USC 112 because the claims are directed to a genus of polypeptides that have not been described in the claims. No description has been provided of all the polypeptide sequences encompassed by the claim. No information, beyond the characterization of the structure has been provided by

applicants which would indicate that they had possession of the claimed genus of polypeptides. The claims do not contain any disclosure of the function of all the polypeptide sequences encompassed, including fragments within the scope of the claimed genus. The genus of polypeptides claimed is a variable genus including peptides which may have different functions. Therefore functionally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the above rejection which was previously directed against claims 21 and 22, applicants have cancelled claims 21 and 22. However, the above rejection is directed to amended/new claims 23, 26-29, 29-31, 33, 45-46.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an

> international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 23-29, 29(misnumbered)-31, 33, 45-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Freeman et al. (Biochem. J. 1998, Vol. 330:1341-1350). This rejection is based upon the public availability of a printed publication. Claims 23-29, 29-31, 33, 45-46 of the instant application are drawn to polypeptides and polypeptides having human heparanase activity and polypeptides comprising fragments of the same, which applicants call as heparanase-II and a composition comprising the same. Freeman et al. disclose a human heparanase enzyme purified from platelet and demonstrate that the purified enzyme is 1700 fold pure and provide a composition comprising the same. The reference does not provide the amino acid sequence of the enzyme. However, Examiner takes the position that the amino acid sequence of an enzyme (a polypeptide) is an inherent charactetistic and therefore as the enzyme in the reference has the same activity as described by the applicants, the enzyme in the reference and the enzyme claimed by the applicants are one and the same. Therefore, Freeman et al. anticipate claims 23-29, 29(misnumbered) -31, 33, 45-46 as written.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

Claims 23, 26-27, 33, 45-46 are rejected under 35 U.S.C. 102(e) as being anticipated by Fiscella et al. (Accession No. AAU07424, 12-18-01 and WO 01/79253, Oct, 2001, filed on 4-11-01 with an effective US filing date 4-18-00, published in English with US as a designated State, Jumbo Document, 308 pages). This rejection is based upon the public availability of a printed publication. Claims 21-23, 26-27 and 33 of the instant application are drawn to a human heparanase, a composition comprising the same, human heparanase comprising amino acids 42-129 or 42-161 of SEQ ID NO:2. Fiscella et al. disclose a human heparanase polypeptide, a composition comprising the same, human heparanase comprising amino acids 42-129 or 42-161 of SEQ ID NO:2 encoded by nucleotides 148-411 or 148-507. Thus Fiscella et al. anticipate claims 23, 26-27, 33, 45-46 of this application as written.

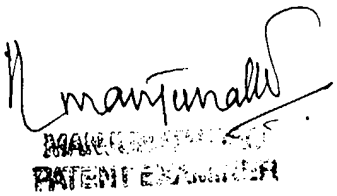
In response to the previous Office action, applicants have filed a declaration under Rule 1.132 to overcome the above rejection. However, such a response, i.e., a Declaration under 37 CFR 1.132 is improper for the above rejection. It appears that applicants intend to overcome the rejction by swearing behind the date of the reference. If applicants intend to swear behind the reference date they need to file a Declaration under 37 CFR 1.131 (see MPEP 715). Therefore applicants need to perfect their Declaration and until such time the above rejection is maintained for reasons of record.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.



Manjunath N. Rao
November 13, 2003